delineated election falls within Group I (claim 37), wherein the antihistamine is fexofenadine HCl form X with cellulose, mannitol, starch and croscarmellose, and the decongestant is a salt of pseudoephedrine with polyvinylacetate and povidone. However, the Examiner has further indicated that claims 18-36 reading on the elected subject matter can be prosecuted with claims 37, and that the remaining subject matter wherein the antihistamine is selected from fexofenadine (excluding HCl in form X), loratadine, terfenadine, cetirizine, or pharmaceutically acceptable salts thereof, and wherein the decongestant is selected from pseudoephedrine (nonsalt), phenylephrine, phenylpropanolamine, or pharmaceutically acceptable salts thereof, are withdrawn from consideration.

Applicants extend their appreciation to the Examiner for examining each of the pending claims 18-37 with respect to the elected subject matter. As claims 18 and 27 are currently generic with respect to the antihistamine and decongestant, Applicants respectfully request that upon allowance of a generic claim, the Examiner withdraws the species election requirement and examines the remaining species for patentability in accordance with MPEP § 809.02(a).

Claim Rejections – 35 USC § 112

Claims 37 and 18-36 reading on claim 37 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement. The Examiner provided two bases for the rejection. First, the Examiner stated:

> The claims are drawn to a composition containing fexofenadine hydrochloride Form X in a bilayer composition with pseudoephedrine. The maintenance of the "Form X' in a composition depends

> unpredictably on its process steps. Any step that dissolves the active compound in its crystalline form would not result in a composition that contains such a *form.* It is noted that on page 10, lines 14-17, it was described: *"Sift Fexofenadine hydrochloride (Form X/A), mannitol, powdered cellulose, crosscarmellose sodium and colloidial silicon dioxide through mesh #20 screen. Sift corn starch iron oxide red through mesh #80 screen. Mix the sifted material in rapid mixer granulator (RMG) for about* 25 *minutes. Mix the obtained dry mix from RMG with isopropyl alcohol to obtain desired wet mass."* The mixing with solvent isopropanyl has been recognized in the prior art to dissolve fexofenadine hydrochloride (See US 2005/0256163, p.8, example 7). Dissolution of the crystalline form will result in a composition containing amorphous fexofenadine hydrochloride not the crystalline form X. To the extent, the dry powder can be directly pressed into tablet, it is noted in preponderance of art that absent of factual evidence, such compression would result in transformation or disappearing of the crystalline form and a Wand's analysis is made below.

The Examiner then stated:

> It is well known in the art, at a given pressure and temperature only one thermodynamically stable crystalline form will exist for a given compound (see encyclopedia supra and US Pharmacopia). It is further well recognized in the art that when a crystalline form for a drug is prepared into a solid formulation, *unless specific and particular* conditions can be described, the "form" is expected to change to the most thermodynamically stable one.
>
> …
>
> The specification provided no description or enablement as to how the crystalline form X can be prepare into a composition which can maintain the particular crystalline structure without the conventional recognized conversion to its thermodynamic form. Preponderance of evidence in the prior art indicated that for a given polymorph, *absent of/actual evidence* the compression process

> as disclosed does not *automatically* keeps the original form in the pharmaceutical composition. Absent of this composition, the bilayer composition with "form X" lacks enablement.

Applicants respectfully traverse these bases for rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See* MPEP § 2163. To satisfy the enablement requirement, the patent specification must contain sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. *See* MPEP § 2163.01.

Regarding the Examiner's first basis for the rejection, the Examiner apparently believes that the process used in Example 1 of the application, wherein the dry mix from the granulator is mixed with isopropanol to obtain a "desired wet mass," would dissolve the fexofenadine hydrochloride form X into the amorphous form. The Examiner relied on US 2005/0256163 for evidence of this transformation.

However, Applicants first note that US 2005/0256163 actually teaches preparation of ***bulk*** fexofenadine HCl form XVI comprising, *inter alia*, dissolution of ***fexofenadine base*** in isopropanol. As such, US 2005/0256163 has no relevance to whether ***granulated*** crystalline ***fexofenadine HCl*** would dissolve by addition of isopropanol.

In addition, the Examiner ignored the teaching in the instant application that isopropanol is added to the dry mix to obtain a "desired wet mass," which is

then dried in fluidized bed drier. *See* page 10, lines 16-18. As one of skill in the art recognizes, obtaining a "desired wet mass" is not equivalent to "dissolution." The Examiner has provided no evidence that the addition of isopropanol to granulated crystalline fexofenadine HCl to achieve a "desired wet mass" results in complete dissolution and loss of all crystalline form. Indeed, earlier patent literature teaches that various polymorphic forms of fexofenadine HCl could be wet granulated with no evidence of loss of crystalline structure. *See, e.g.*, U.S. Patent No. 5,738,872, col. 14, lines 43-62. To the extent any fexofenadine HCl is dissolved into amorphous form, that portion is outside the scope of the claims. *See Ex parte Li*, Appeal No. 2007-1348, for U.S. Pat. Appl. No. 10/650,253, at 9 (BPAI 2007) ("A mixture of (1) azithromycin, resulting from de-crystallization of form F when placed in water, and (2) water are not covered by, and do not fall within the scope of claim 125."); *Ex parte Glover*, Appeal No. 2006-2861, for U.S Pat. Appl. No. 10/007,272, at 5 (BPAI 2007) ("[T]he claimed invention differs from the disclosure of Chamberlain in that the claims specifically recite a *crystalline* form of the compound. The rejection improperly ignores this element of the claims.") (emphasis in original). Furthermore, even if in some embodiments of fexofenadine hydrochloride within the scope of the examined subject matter did truly lose all crystallinity, the compositions defined by the claims would still be useful, since it is not disputed that the specification teaches how to make and use pharmaceutical compositions comprising fexofenadine hydrochloride form X. *See Li*, *supra* ("Even if we assume that some embodiments within the scope of claim 125 might be non-enabled, the composition defined by claim 125 would still

be useful and the specification otherwise advises one skilled in the art how to make and use substantially pure [crystalline] azithromycin Form F mixed with other carriers and diluents.").

Regarding the Examiner's second basis for the rejection, the Examiner apparently believes that processing crystalline fexofenadine HCl form X into a pharmaceutical dosage form could result in the transformation into a different crystalline form. The Examiner cited a number of references to show that it is generally known that the processes involved in tablet preparation may change a pharmaceutical compound's polymorphic form.

However, Applicants note that nothing in the examined subject matter requires that crystalline form X be maintained indefinitely in the composition, or that it even be the only form present in the composition, and it is error for the Examiner to read such limitations into the claims. Applicants specifically provide examples showing the preparation of pharmaceutical compositions comprising crystalline fexofenadine HCl form X, thereby adequately describing and enabling the examined subject matter. *See Ex parte Reddy*, Appeal No. 2009-000439, for U.S. Patent Application No. 10/505,826, at 23 (BPAI 2009) ("[B]ecause the Specification lists the solid formulations and excipients suitable for the crystalline forms X and Y we agree . . . that a person of ordinary skill in the art would have understood Appellants to be in possession of the [claimed] subject matter . . . [and] that any experimentation that would be required to prepare the claimed pharmaceutical compositions would be routine in nature, rather than undue."). In fact, the instant specification specifically teaches that "polymorphic conversion is

most common still challenging product quality," but that the examples are "robust enough to assure the product quality characteristics in routine manufacturing." *See* page 9, line 35 to page 6, line 6. The Examiner cited no direct evidence to the contrary. *See Reddy*, *supra* ("While it may be true that polymorphic forms can undergo undesirable changes when formulated into dosage forms, the Examiner has not explained . . . why the *claimed* crystalline forms would be subject to these problems.") (emphasis in original).

The references relied on by the Examiner actually support the conclusion that the examined subject matter is enabled, providing guidance to one of skill in the art of pharmaceutical formulations. *See Reddy*, *supra* ("If anything, the disclosures cited by the Examiner suggest that a skilled artisan knew what actions to avoid when formulating sensitive polymorphic forms, and if encountering problems, what actions might be taken to rectify them.") Furthermore, several of the references cited by the Examiner explain that polymorphic transformation can be very slow (on the order of years) owing to the relative stability of the metastable form. For example, Muzaffar notes at page 60:

> When the rate of conversion of a metastable form is so slow as to be negligible, the solubility of the compound will be maximal and will have a faster rate of dissolution and hence absorption. This biopharmaceutical property of the polymorphs could be explained for achieving better results in the formulation of drugs, especially in the unit dosage forms of the drugs.

Thus, even assuming that fexofenadine HCl form X was subject to polymorphic conversion (mere conjecture at this point), the possible transformation at some point in the future does not detract from its utility while in

the claimed form. Again, any fexofenadine HCl not having the form X crystal structure is simply outside the scope of the claims. As MPEP 2164.01(b) states:

> Naturally, for unstable and transitory chemical intermediates, the "how to make" requirement does not require that the applicant teach how to make the claimed product in stable, permanent or isolatable form. *In re Breslow*, 616 F.2d 516, 521, 205 USPQ 221, 226 (CCPA 1980).

Since the specification teaches how to make and use pharmaceutical compositions containing fexofenadine HCl form X, Applicants submit that claims 37 and 18-36 reading thereon meet the written description and enablement requirements, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 USC § 103

Claims 37 and 18-36 reading on claim 37 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over MacLaren et al., US 6,039,974 ("MacLaren"), in view of Pharmapedia, 2009 ("Pharmapedia") or Ahjel, 2008 ("Ahjel"), further in view of Edgren et al., US 6,210,712 ("Edgren") and Buhler, 2009 ("Buhler"). According to the Examiner, MacLaren discloses bilayer compositions containing a layer of antihistamine fexofenadine in immediate release formulation and a layer of pseudoephedrine in sustained release formulation. The Examiner acknowledged that MacLaren does not disclose mannitol, but asserts that Pharmapedia or Ahjel teach that mannitol and lactose are optional choices of diluent. The Examiner also acknowledged that MacLaren does not disclose pyrrolidone and vinyl acetate, but asserted that Edgren and Buhler teach pyrrolidone and vinyl acetate for sustained release.

Applicants respectfully traverse this basis for rejection.

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. *See In re Fine*, 837 F.2d 1071, 1073 (Fed. Cir. 1988). In so doing, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), *viz.*, (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the art. "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Furthermore, although the analysis need not identify explicit teachings directed to the claimed subject matter, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). As such, "'there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The § 103 rejection is based primarily on the Examiner's belief, discussed above, that the instant specification fails to adequately describe and enable pharmaceutical compositions comprising fexofenadine HCl form X. Specifically,

the Examiner states that elected active ingredient, fexofenadine HCl form X, in its dissolved form, would read on the compositions disclosed in MacLaren.

However, as discussed above with respect to the written description and enablement rejections, no evidence has been provided to support the conclusion that the addition of isopropanol to granulated crystalline fexofenadine HCl form X to achieve a "desired wet mass" results in complete dissolution and loss of all crystalline form. As noted above, earlier patent literature teaches that various polymorphic forms of fexofenadine HCl could be wet granulated with no evidence of loss of crystalline structure. Reading MacLaren to cover the claimed composition improperly ignores a critical limitation of the examined subject matter, namely that the fexofenadine HCl be crystalline form X. *See Glover*, *supra* ("[T]he claimed invention differs from the disclosure of Chamberlain in that the claims specifically recite a *crystalline* form of the compound. The rejection improperly ignores this element of the claims.") (emphasis in original). Again, to the extent any fexofenadine HCl is dissolved into amorphous form, that portion is outside the scope of the claims. *See Li*, *supra* ("A mixture of (1) azithromycin, resulting from de-crystallization of form F when placed in water, and (2) water are not covered by, and do not fall within the scope of claim 125.").

Furthermore, MacLaren's recitation of fexofenadine HCl would not have suggested the specific crystalline form under examination. Although the polymorphic nature of fexofenadine HCl is known, nothing in MacLaren, or the art in general relied on by the Examiner, would have suggested fexofenadine HCl form X, or a method for its preparation. The mere existence of other polymorphs

is not sufficient to support a *prima facie* case of obviousness under these circumstances – the prior art must suggest the ***specific*** polymorph that is claimed. *See Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 892 F.2d 1050, 1989 WL 147230 (Fed. Cir. Dec. 8, 1989) (unpublished decision) ("The law of § 103 requires quite a different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to ***make the Bouzard monohydrate, based on the prior art***.") (emphasis added); *Ex parte Reddy*, Appeal No. 2009-002678, for U.S. Patent Application No. 10/816,798, at 8 (BPAI 2009) ("The other references cited by the Examiner disclose that many pharmaceutical compounds exhibit polymorphism and can exist as more than one crystalline form. However, the Examiner has pointed to no disclosures in the prior art that support a conclusion that the cited references would have suggested the ***specific crystal form*** of Donepazil hydrochloride that is claimed.") (emphasis added); *Ex parte Havens*, Appeal No. 2001-0091, for U.S. Patent Application No. 08/732,254, at 6 (BPAI 2001) ("The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the ***specific S and T crystal forms*** that are the subject of the instant claims.") (emphasis added).

Since none of the references relied on by the Examiner would have suggested fexofenadine HCl form X, Applicants submit that claims 37 and 18-36

reading thereon are not unpatentable over MacLaren, in view of Pharmapedia or Ahjel, further in view of Edgren and Buhler, and reconsideration of this basis for rejection is respectfully requested.

CONCLUSION

It is believed that claims 37 and 18-36 reading thereon are now in condition for allowance. Applicants respectfully request that the Examiner withdraws the species election requirement and passes the remaining species to allowance. Please contact the undersigned if any further issues remain to be addressed in connection with this submission.

Date: October 20, 2009

Respectfully submitted,

By: /Kenneth M. Zeidner, Reg. No. 64700/
Kenneth M. Zeidner
Reg. No. 64,700
Attorney for Applicants

Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd.
Seventh Floor
Bridgewater, NJ 08807-2862
Tel. No.: 908-203-6504
Fax No.: 908-203-6515